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PROGRESS REPORT

of a study on

Relationship of airborne manganese exposure to neurobehavioral and health status of adults

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Introduction

Exposure Background:

In 2000, the Agency for Toxic Substances and Disease Registry (ATSDR) initiated a public health assessment for the Marietta Air Emissions Site (Ohio). Air monitoring in the region identified airborne manganese (Mn) as the main environmental exposure of concern.

Eramet Marietta, Inc (EMI) is the major historic producer of Mn ferroalloys in the region and is one of the largest Mn-manufacturing facilities in the world. Historically, Eramet Marietta Inc. (EMI) ranks first in total air releases of Mn and Mn compounds among all U.S. facilities reporting to the USEPA Toxic Release Inventory (TRI). The ATSDR has determined that long-term ambient Mn concentrations in the area exceed the USEPA reference concentration (RfC = 0.05 µg/m3) and minimal risk level (MRL = 0.04 µg/m3).

Human Exposure to Manganese:

In the occupational health literature there are many reports of workers exposed to Mn with adverse health effects. Miners and chemical workers who are over-exposed to Mn, a major component in iron/steel welding fumes, are known to be at risk for developing a pattern of signs and symptoms showing a decline in psychiatric health and cognitive ability and a movement disorder similar to Parkinson's disease (PD) (i.e. a disturbance of gait, loss of balance, and dystonia, bradykinesia, tremor) (Bowler, Roels, et al., 2007).

Environmental studies of airborne Mn have been relatively rare and results of a select few studies have been published. This is the 1st comprehensive environmental study of Mn-exposed adults in the U.S.

The current study aimed to answer the following questions:

- Is there is a relationship of Mn levels in blood (Mn/B) (internal) or Mn levels in air (Mn/air) (external) and neurobehavioral function in adults?

- Does the neurobehavioral function of a group of Mn-exposed adults differ significantly from that of a demographically similar group of minimally exposed adults?

Design

This study used a **cross-sectional control/exposed** design of 100 Mn-exposed and 100 control **(low-**exposed) adults between the ages of 30-75 years. It includes air monitoring, biomarkers, health, neuropsychological, neurological, and sensory assessments of participants from both groups.

Recruitment procedure

Participants were randomly selected using property tax records, from the Mn-exposed town of Marietta, and the low-exposed comparison town – Mt. Vernon (OH). A total of 1,732 participants from Marietta and 2,207 from Mt. Vernon were selected using a list of random numbers and sent recruitment letters describing the study. A response card, stamped and addressed to the study office, was included for the potential participant to complete and return if they were interested in participating. Of the 3,939 letters sent, 308 were undeliverable and returned (160 from Marietta, 148 from Mt. Vernon). Two-hundred seven participants returned response cards indicating interest (106 from Marietta, 101 from Mt. Vernon. Researchers also attempted to contact by telephone all potential participants who were sent letters and did not return the response card and asked if they were interested in study participation. All participants who indicated interest in the study (215 from Marietta, 220 from Mt. Vernon, for 435 total), either through email, response cards, or when called on the telephone, were given a screening questionnaire with the exclusion criteria. Of these, 65 from Marietta were excluded, as were 95 from Mt. Vernon. One-hundred participants from each town were scheduled for testing, along with 5 alternates for each town. One-hundred participants from Marietta and 91 from Mt. Vernon were tested. One participant tested in Mt. Vernon did not meet to inclusion criteria, and was excluded from analyses. Participants were given $50 gift certificates for their participation, and will be given feedback of their performance on the various tests.

Testing procedure

Dr. Rosemarie Bowler was successful in obtaining the collaboration and participation of Dr. Harry Roels (blood drawing), Dr. Yangho Kim (neurology and UPDRS) and Dr. Nadia Abdelouahab (CATSYS). Two neuropsychologists and 6 trained graduate students administered the neuropsychological tests. The battery included tests that have been shown to be sensitive to Mn exposure, including measures of Cognitive flexibility (ROCF, Trails), Information Processing (Stroop), Working Memory and Attention (ACT), Memory (NAB Memory Module), Visuomotor tracking speed (Digit Symbol Coding), Verbal skills (Similarities, Animal Naming), Motor dexterity and strength (Fingertapping, Grooved Pegboard, Dynamometer), and tremor (CATSYS, UPDRS). In addition, work histories and health questionnaires were administered, and blood was drawn and analyzed for levels of Mn, Cadmium, Mercury and Lead in blood, and Ferritin in Serum.

Exposure assessment

Blood samples from participants were analyzed at the CDC National Laboratory for levels of manganese, cadmium, lead, and mercury. Serum samples were analyzed for levels of ferritin – and indicator of iron store in the body.

Air dispersion modeling was conducted using emissions information, receptors, and meteorological data to calculate estimated Mn concentrations near various

residences in Marietta. This was used to create a hazard quotient (a ratio of modeled concentrations to the Mn reference concentration) and a cumulated exposure index (CEI – the product of modeled concentration and duration of residence in Marietta), two ways of estimating a participant's exposure to airborne Mn.

Results

Levels of Mn in blood ranged from 3.75 to 24.6 µg/L, with a mean level of 9.57 µg/L. Concentrations of Mn in air ranged from .89 to 41.22 µg/m^3, with a mean of 6.67 µg/m^3Hazard quotients ranged from .77 to 19.17, with a mean of 3.69.

No significant differences between the towns were found for any neurobehavioral tests, which included tests of motor speed, motor strength and tremor, attention and immediate memory, switching categories and divided attention, visual delayed memory, and verbal delayed memory. Scores in both towns were within the average range.

Though there was not a consistent relationship between levels of Mn in blood and neurobehavioral performance (in either town), higher exposure to Mn in the air (hazard quotient and CEI) was related to worse performance on some tests, particularly tests of executive functions.

No significant differences were found between the towns on mood disturbance, except for levels of phobic anxiety being higher in Marietta. Overall, there was not a consistent relationship between levels of Mn in blood and mood, though higher hazard quotients were related to higher phobic anxiety and higher CEI was related to higher obsessive-compulsive, anxiety, phobic anxiety, and paranoid ideation symptoms.

There were no significant differences between participants of the two towns in the percent of people reporting poor or fair health, the average number of poor physical or mental health days in a month, the percent of adult smokers, the prevalence of adult obesity, or the prevalence of illnesses categorized into ICD-9 categories. Some symptoms were significantly more frequently reported in Marietta: changes in sense of smell or taste, headaches overall, headaches in the presence of gas, headaches in the presence of paint, tightness of facial muscles, feeling anxious, feeling irritable, changes in personality, excessive perspiration, fever or chills, and nausea.

Mn in blood was related to more frequent endocrine and psychological illness in Marietta, and rigidity (stiffness) in the whole group (Marietta + Mt Vernon). The hazard quotient was related to excessive perspiration but showed no consistent relationship with illnesses or other symptoms. The CEI did not show consistent relationship with illnesses or symptoms.

On a neurological examination, the UPDRS, Marietta participants had slower movement and motor speed than Mt. Vernon participants. No relationship between exposure variables were found with UPDRS scores.

There was no difference in Mn intake in diet between the two towns.

A reliability study for self-reported medication use is in progress.

Conclusion:

Overall, results of this epidemiologic study using random sampling did not support findings of adverse health effects from levels of Mn in air and levels of Mn in blood in the town of Marietta. This is supported by the lack of differences between Marietta and Mt Vernon on neurobehavioral tests. Overall test results are within the average range of the general population.

Prospective Plans:

Year 2:

1. The data analyses will all be confirmed with additional analysis to confirm reproducibility and accuracy of the data analyses.
2. More advanced analyses, such as structural equation modeling will be performed together with Dr. Long Ngo who will travel to meet the investigators.
3. Additional subgroup analyses will be explored and performed
4. Once the serum Mn lab analysis become available from the EPA laboratory, multiple analyses of biomarkers will be carried out. Mn in blood and Mn in serum will be compared
5. Possible production data from Eramet, already received for years 2007, 2008 and earlier years will be explored as additional data to compare the modeled air Mn levels.
6. Meeting with Dr. Yangho Kim summer 2010 in the research office or during a conference, to discuss his draft on the UPDRS findings.
7. Additional manuscripts will be prepared by the P.I., and her collaborators, on
    - Gender findings of biomarkers
    - Relationship of UPDRS and Neuropsychological Motor findings
    - Neuropsychological findings of Mn in ambient air exposed adult residents
    - Manuscript describing the methods and results of this study, to include health questionnaire, illness and symptoms, and diet questionnaire
    - Reliability of Medication self report of adult residents over 2 time periods
    - Results of biomarkers used in this study
    - Mood as a mediator of Executive function and Mn exposure
    - Gender and Mn exposure, pre- and post menopausal status and Mn and Ferritin

Future Presentations

1. A symposium will be presented at the 26th International Neurotoxicology Conference, June 8th, 2010 in Portland, OR including the following presentations prepared with data from the study:

Methodological aspects of an epidemiologic study of adults living near a Mn point source, Rosemarie M. Bowler, Y. Kim, L. Ngo, and H. A Roels.

Relationships between mood and neuropsychological performance in adults with environmental exposure to manganese, Harris, M.

2. Dr. Bowler is giving a presentation to the Marietta community, June 24th, 2010 in Marietta, OH, entitled: **Health Study of Manganese Exposure of Adults in Marietta & Mt. Vernon, Ohio: Preliminary Results.**

3. Dr. Bowler is giving a presentation to the Ohio Department of Health, June 24th, 2010 in Columbus, OH, entitled: **Relationship of residential airborne manganese exposure to neuropsychological, neurological and health status of adults**

4. Dr. Bowler will submit a presentation on the overall results at the 13th Meeting of the International Neurotoxicology Association, June 5th – 10, 2010, Xian, China. Highlights will be the neurotoxicolohgical aspects of the study.

5. Dr. Bowler and her colleagues/collaborators will submit presentations at the International Neuropsychological Society meeting in Boston, Mass in February 2011, on the neuropsychological test results in relation to Mn exposure.

6. A proposal has been submitted to conduct the identical study in residents near a plant in East Liverpool, OH, where at the maximum levels of airborne Mn compared to Marietta are 50X higher, as described in a current health consultation report. Ohio EPA identified the S.H. Bell company, which stores and packages primarily raw metals from all over the world. S.H. Bell operations store, transfer and warehouse ferrous and nonferrous materials for industry. Their sites process, dry, crush, screen and package materials which are transported with river barge, truck and rail. Three ambient air monitors have collected measurements in this community for the last 10 years. If this project is funded, the results will be added to those of the current study, and three-way comparisons on participants from the three towns will determine the effects of a gradient of exposure and if there are significant relationships between Mn in air and health effects.

7. A final report will be issued at the end of the present funding period of this co-operative agreement prior to June 30, 2011.